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Better Long-Term Prognosis: Comparison Between Surgery and TACE as Initial Treatment for Operable Huge HCCs (≥10 cm) After More Than 5 Years of Follow Up

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The objective of this study was to research the long-term survival difference between surgery and transarterial chemoembolization (TACE) for operatable hepatocellular carcinoma (HCC) ≥10 cm. Little data are available comparing surgical resection with nonsurgical treatment in the management of very large HCCs (≥10 cm). We proposed to directly compare patients' 5-year survival rates after surgical resection or TACE of these tumors. Between January 2004 and June 2009, 16 patients with HCCs ≥ 10 cm underwent hepatic resection, and 9 received TACE. The patients were followed for 5 years or longer. The median follow-up period was 55.6 months. The median survival time was significantly longer in the resection group than in the TACE group (30.2 versus 9.33 months; $P = 0.05$). The 1-, 3-, and 5-year survival rates for patients in the resection group also were significantly better than for patients in the TACE group (operative group: 57.8%, 36.1%, and 28.9%, TACE group: 33.3%, 11.1%, and 0%, respectively). Surgical resection as initial treatment for resectable HCCs ≥10 cm has a better long-term survival outcome than does TACE.

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Surgical treatment for hepatocellular carcinoma (HCC), including liver resection and transplantation,[1] is the first therapeutic choice for the cancers. However, patients with HCC ≥10 cm often are treated with nonsurgical approaches because of the presumed higher risks associated with surgery.[2] However, the reported 5-year survival rate after transarterial chemoembolization (TACE) for very large HCCs is only 7% to 10%.[3–5] Thus, liver resection appears to be associated with better prognosis than TACE, with 5-year survival rates reaching 35%.[5,6] However, few data are available on the long-term survival of patients with very large HCCs treated with surgical resection compared directly with TACE.

In this study, we proposed to determine the long-term outcome of patients with HCC ≥10 cm treated with surgical resection or TACE. We also analyzed risk factors for disease-specific overall survival after the 2 treatments.

Materials and Methods

Patients

We performed a retrospective analysis of 125 patients with HCC ≥10 cm admitted to the Da-lin Tzu-chi General Hospital between January 2004 and June 2009. Before surgery, surgeons evaluated all patients. The resectable lesions were identified as adequate liver reservation after necessary liver resection for tumor clearance. Sixteen patients underwent liver resection and 9 received TACE. One hundred patients were excluded because of having stage IV liver disease (20), having received chemotherapy and/or radiotherapy (3), having poor liver disease (27), or for personal reasons (50). The patients' demographics, characteristics of the tumor, treatment characteristics, and disease-specific overall survival rates were evaluated.

After being discharged, patients were regularly followed in an outpatient clinic, with physical examination, ultrasound, annual serial computer tomography scans, and the measurement of α-fetoprotein concentrations every 3 months for 2 years and every 6months in the subsequent years. Recurrence of HCC was identified by the presence of new or growing lesions on imaging studies, with appearance typical of HCC, or suspected lesions with rising α-fetoprotein concentrations. For atypical hepatic lesions, we performed confirmatory biopsies. The choice of treatment for HCC recurrences included local treatment, TACE, transarterial embolization, or repeated resection, with the decision based on the patient's condition and disease severity.

Statistical analysis

Patient demographics, characteristics of the tumors and surgical procedure, and treatment characteristics were evaluated. Variables, including age, sex, comorbidities, hepatitis serology, α-fetoprotein, other usual laboratory data, Child-Pugh class, and model for end-stage liver disease (MELD) scores were analyzed. The tumor characteristics, including solitary or multiple lesions, preoperative portal vein thrombosis that was diagnosed by imaging, operative variables, mortality, morbidity, severity of morbidities, and postoperative tumor characteristics were also analyzed. All patients were restaged pathologically and clinically restaged according to the seventh edition of the American Joint Commission on Cancer (AJCC).

Comparisons between groups were performed with the χ^2 test for categorical variables and Student *t*-test for continuous variables. Disease-specific overall survival was determined by use of the Kaplan-Meier method and compared by use of the log-rank test. $P < 0.05$ was considered statistically significant. All variables that were significantly associated with overall survival were entered into a backward stepwise Cox proportional hazards model for significant effects. $P < 0.05$ was considered statistically significant.

Results

Clinical features and tumor characteristics of the 2 groups of patients are summarized in Table 1. No differences between the hepatic resection group and the TACE group were identified. The diseased-specific overall survival curves of the 2 patient groups are illustrated in Fig. 1. The median survival time was significantly longer in the resection group than in the TACE group (30.2 versus 9.33 months; $P = 0.05$). The 1-, 3-, and 5-year survival rates for patients in the resection group were 57.8%, 36.1%, and 28.9%, respectively, which were significantly

Table 1 Clinical features of the hepatic resection group and the TACE group

Variables	Resection (n = 16)	TACE (n = 9)	*P* value
Clinical Characteristics			
Age (y)	62.4±17.0	60.8±12.7	0.80
Sex			1
Male	15	8	
Female	1	1	
Virus type			0.79
Non-B, non-C	4	1	
HBV	9	5	
HCV	2	2	
HBV + HCV	1	1	
Child-Pugh class			1
A	13	8	
B	3	1	
MELD score	8.09±1.68	8.33±2.00	0.73
Tumor-related factors			
Tumor sizes (mm)	100-180	100-150	
Tumor numbers			0.21
Solitary	13	5	
Multiple	3	4	
BCLC status			0.67
B	12	6	
C	4	3	
Tumor stage (AJCC 7th)			0.27
Stage II	7	3	
Stage IIIa	2	4	
Stage IIIb	5	2	
Stage IIIc	2	0	
Tumor size (mm)	132.1±28.0	116±16.9	0.19

AJCC, American Joint Committee on Cancer; BCLC, Barcelona-Clinic Liver Cancer; HBV, hepatitis B virus; HCV, hepatitis C virus.

better than for patients in the TACE group (1-, 3-, and 5-year survival rates of 33.3%, 11.1%, and 0, respectively). Most patients in the TACE group died within 20 months, but 1 patient, who underwent palliative hepatic resection after 3 courses of TACE, survived 57 months.

The details of the 16 patients in the surgical group are listed in Table 2. In summery, patient age was

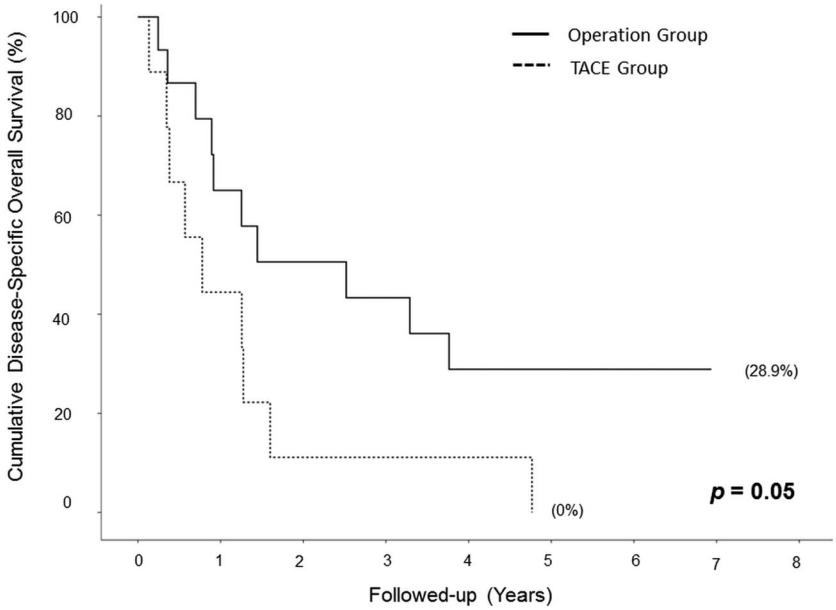

Fig. 1 Disease-specific overall survival of patients with HCCs ≥10 cm from the hepatic resection group and TACE group. The 1-, 3-, and 5-year survival rates of the HR group were 57.8%, 36.1%, and 28.9%, and from the TACE group were 33.3%, 11.1%, and 0, respectively.

Table 2 Details of patient of operation group

No.	Sex	Age (y)	Hepatitis	CP class	BCLC	MELD score	Tumor character	Size (mm)	PVT on image	Stage	Operation
1	F	72	HBV+HCV	B	B	12	Left, single	115	0	3C	L't lobectomy
2	M	60	HCV	B	B	11	Right, single	180	0	3B	Extended R't lobectomy
3	M	69	Non	A	C	8	Right, single	180	1	3B	Extended R't lobectomy
4	M	46	HBV	A	C	9	Right, single	155	1	3B	Extended R't lobectomy
5	M	78	Non	A	B	6	Right, single	107	0	2	Extended l't lobectomy
6	M	76	Non	A	B	7	Right, single	100	0	2	Trisegmentectomy (4+5+8)
7	M	57	HBV	A	B	6	Right, single	138	0	2	Extended R't lobectomy
8	M	60	Non	B	B	9	Right, single	170	0	3C	Extended R't lobectomy
9	M	34	HBV	A	B	8	Right, single	130	0	2	Extended R't lobectomy
10	M	67	HCV	A	B	7	Caudate, single	127	0	2	Extended l't lobectomy
11	M	61	HBV	A	B	8	Right, multiple	100	0	3A	Bi-segmentectomy(7+8) and enucleation(4)
12	M	54	HBV	A	B	6	Right, single	102	0	2	Trisegmentectomy (5+6+7)
13	M	62	HBV	A	C	8	Right, single	140	1	3B	Extended R't lobectomy
14	M	51	HBV	A	B	8	Right, single	118	0	2	Trisegmentectomy (6+7+8)
15	M	79	HBV	A	B	7	Right, multiple	105	0	3A	Trisegmentectomy(5+6+7) and Enucleation(8)
16	M	46	HBV	A	C	7	Bilateral, multiple	147	1	3B	L't lobectomy+Enucleation (7)

E, extrahepatic recurrence; L, intrahepatic recurrence.

between 34 and 79 years. Most of the tumors were located at the right lobe (13 of 16). Most of them were a single tumor. The tumor size was between 10 and 18 cm. The only mortality was caused by liver failure. There were 4 morbidities including pneumonia in 2 patients and bile leakage in 2 patients. The follow-up period was between 0.2 and 83.2 months. Only 1 patient was still free of recurrence after a 73.1-month follow-up period. Most recurrences were located in the liver. However, 6 of them were combined with extrahepatic recurrence including the lung (5 patients) and spleen (1 patient). Most of the patients with recurrence received TACE as their primary treatment. Only 1 patient received re-resection and was still alive after an 83.2-month follow-up.

We analyzed prognostic factors for the 25 HCC patients (Table 3). Univariate analysis identified 3 negative prognostic factors for overall survival including age <50 years, preoperative portal vein thrombosis, and TACE.

Discussion

This study had 2 objectives: (1) determine the long-term outcome of patients with HCC ≥10 cm treated with surgical resection compared with TACE and (2) analyze risk factors for disease-specific overall survival after the 2 treatments.

Previous studies had suggested that resection is superior to TACE in the treatment of very large HCCs, but ours is the first study to our knowledge that directly compared the 2 treatments with follow-up for as long as 5 years. Min *et al*.[7] directly compared the prognosis between surgery and TACE and found significantly higher 1-, 2-, and 3-year overall survival rates for operated patients than for TACE-treated patients followed for a median time of 14.5 months. Other studies have reported that the 5-year survival rate of patients with HCCs ≥10 cm

Table 3 Prognostic factors for patients with HCC ≥10 cm

Variables	Univariate Analysis (*P* value)
Clinical characteristics	
Male:female	0.824
Age < 50 years[a]	0.020
Diabetes mellitus	0.725
Hypertension	0.104
Non-B, non-C infection	0.888
HBV + HCV infection	0.824
BCLC stage	0.183
Child-Pugh score	0.713
Tumors factors	
Solitary or multiple	0.552
*Portal vein thrombosis (+)	0.040
A-fetoprotein ≥200 ng/mL	0.182
AJCC 7th stage	0.256
Operation or TACE[a]	0.050

[a]$P \leq 0.05$.

Table 2 Extended

Operative time (min)	Blood loss (mL)	Free margin (mm)	ICU stay (days)	Hospital stay (days)	Mortality/ Morbidity	Follow-up (mo)	Recurrence (mo)	Disease-specific death	Type of recurrence	Extrahepatic recurrence	First recurrence treatment
270	3000	0	4	18	—	45.2	7.2	Y	L+E	Lung	TACE
695	2200	0	6	16	Bile leak	17.3	7.4	Y	L+E	Spleen	TACE
335	2600	4	3	10	—	11.0	6.6	Y	L+E	Lung	TACE
320	1600	0	2	12	—	15.0	3.4	Y	L+E	Lung	TACE
235	1000	1	8	14	Pneumonia	73.1	—	N	—	—	—
270	750	0	3	12	—	8.4	3.8	Y	L	—	TACE
235	1800	9	3	13	—	30.2	6.5	Y	L	—	TACE
480	5300	3	5	5	Mortality	0.2	—	Y	—	—	—
285	1300	<1	1	10	—	5.1	2.1	—	L	—	TACE
900	3650	<1	16	28	Pneumonia	77.7	21.2	—	L	—	TACE
300	2200	2	2	14	—	83.2	43.4	—	L	—	Re-resection
255	950	3	2	10	—	10.7	9.3	Y	L+E	Lung	TACE
235	2500	Not free	4	12	—	4.3	2.1	Y	L	—	TACE
240	300	10	1	12	—	39.5	8.6	Y	L	—	TACE
175	1200	4	2	11	—	71.9	3.3	—	L	—	TACE
335	2000	<1	0	10	—	2.9	2.0	Y	L+E	Lung	TACE

who underwent surgical interventions varied from 16.7% to 54.0%,[2,5,8–12] whereas the reported 5-year survival rate of TACE-treated patients for similarly large HCCs is less than 10%.[3,4] Yamashita *et al*.[5] and Mok *et al*.[13] have reported that the 5-year survival rate in patient with HCC ≥10 cm who had resection was significantly better than in those who did not have resection.

We first found that patients who had surgical resection had a significantly better overall survival that did patients treated with TACE (median survival, 30.2 versus 9.33 months; $P = 0.05$). Survival rates at 1, 3, and 5 years also were superior in the patients who had resection (1YOS: 57.8% versus 33.3%, 3YOS: 36.1% versus 11.1%, and 5YOS: 28.9% versus 0). The 2 patient groups were well matched for age, sex, comorbidity, hepatitis virus type, liver function, tumor characteristics, and tumor stage. Most patients in the TACE group died within 20 months. Only 1 patient in the TACE group who survived more than 20 months received surgery following the first TACE treatment. Therefore, we considered that tumor resection is still the best treatment policy for huge HCCs. Surgeons should carefully evaluate these patients. Once the patient was fit for surgery, surgical resection should be done for the best prognosis for patients.

However, another concern is perioperative morbidity and mortality. The technical demand is higher for resection of huge HCCs, and the following mortality and morbidity rates may be possibly higher than surgical resection for smaller HCCs. The reported mortality for resection of HCCs ≥10 cm is 2% to 15%,[5–7] and the complication rates were about 24.5% to 50%.[5,6] Previously, our group compared surgical results including postoperative mortality, incidence, and severity of morbidity between operation for huge HCC and smaller (less than 10 cm) HCCs.[14] Although higher perioperative stress included longer operative time, more blood loss, and more blood transfusions, there was no difference in perioperative mortality or rates and severity of complications between surgery for huge HCCs or smaller HCCs. In our opinion, although resection is technically demanding, the mortality and morbidity rates in patients operated for HCC ≥10 cm compare favorably with those operated for HCCs <10 cm.

Our study has limitations. First, it is a retrospective nonrandomized study, and the choices of TACE or surgery were based on surgeons' evaluation and the patients' clinical condition. Second, the sample size is relatively small. Despite the small size, however, the survival difference between the TACE group and surgical group is significant. Moreover, the length of follow-up time for our study is more than 5 years. The follow-up period of a previously published similar study[7] is 3 years. Further larger sample, multicenter, and even randomized control trials are necessary to corroborate the findings here.

Conclusions

We conclude that surgical resection for HCCs ≥10 cm appears superior to TACE as it provides a higher rate of longer long-term survival. Although resection is technically demanding, the operation is still safe for selected patients. Patients, especially young patients, with advanced-stage tumors and unfavorable biological behavior of the tumor should not necessarily be excluded from undergoing liver resection with the possibility of a cure. However, larger series should be studied to validate our results.

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